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NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
WILSON, MICHAEL C	
ART UNIT	PAPER NUMBER
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,612	OKANO ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9-5-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-20 are pending and under consideration.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-11, 13-20 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The animal of claims 1-11 and 13-20 encompasses humans, which is non-statutory subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making an animal having transplanted cancer cells comprising i) preparing a cell culture support coated with poly N-isopropylacrylamide, ii) cultivating cancer cells on the cell culture support at a temperature in which the cells adhere and grow, iii) decreasing the temperature so that the cancer cells detach from the support, and iv) transplanting the detached cancer cells to an animal, does not reasonably provide enablement for any polymer that changes its hydration force as broadly claimed. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 1 is drawn to a method of making an animal having transplanted cancer cells comprising i) preparing a cell culture support coated with a polymer that changes its hydration force in a temperature range of 0-80˚ C, ii) cultivating cancer cells on the cell culture support at a temperature in which the polymer has weak hydration force, iii) adjusting the temperature so that the polymer has a stronger hydration force and the cultured cancer cells detach, and iv) transplanting the detached cancer cells to an animal.

The specification states JP 05/192138 taught a method of "skin cells cultivation comprising the steps of preparing a cell culture support which has a surface of its base coated with a polymer having an upper or lower critical temperature for dissolution in water in a range of 0-80°C, cultivating skin cells on the cell culture support at a temperature not higher than the upper critical temperature for dissolution or at a temperature not lower than the lower critical temperature for dissolution, and thereafter adjusting the temperature to above the upper critical temperature for dissolution or below the lower critical temperature for dissolution, whereby the cultured skin cells are detached. This method depends on temperature adjustment for detaching the cells from the culture base coated with the temperature-responsive polymer."

Example 1 describes a "cell culture base was coated with the temperature-responsive polymer poly(N-isopropylacrylamide) in an amount of 2.0 μg/cm2 and the cancer cells NCI-H460 was cultivated (2 x 104 cells were seeded; 37°C in 5% C02).

Three days later, the cancer cells (NCI-H460) on the culture base were confirmed to have become confluent; thereafter, a cultured cell moving jig comprising a polyacrylic plate coated with a fibrin gel was gently placed over the cultured cell sheet so that the cultured cancer cells adhered to it; then, the cell culture base was cooled at 20°C for 60 minutes. After the cooling, the detached cell sheet was collected from the jig together with the fibrin gel and a piece of the gel with the adhering cell sheet (7 mm x 17 mm x 2 mm; 5 x 10^5 cells) was transplanted subcutaneously to the back of each of 10 nude mice.

The specification and the art do not teach any polymers that change hydration force in a temperature range of 0-80 degrees C as required by the claim other than poly(N-isopropylacrylamide). In fact, the specification does not enable those of skill to determine when a polymer's "hydration force" was in a range that allowed it to attach and grow cells and when it was in a range that caused it to detach. It would have required those of skill undue experimentation to determine other polymers that would culture cells on the polymer at one temperature then detach the cells at a different temperature as claimed. Therefore, the claims should be limited to using poly(N-isopropylacrylamide).

The claims encompass making any species of animal. Claim 12 is limited to making a nude mouse, rat, mouse, guinea pig rabbit. The specification suggests making a nude mouse, rat, mouse, guinea pig rabbit and exemplifies making a nude mouse. However, for the animal to be a model of human cancer, it must comprise human cancer cells. For the animal to support the growth of human cancer cells, it

must not reject the cells. The only means described for maintaining human cancer cells in an animal model is if the animal is immunocompromised, and the only immunocompromised animal described by applicants is a nude mouse. If the animal is not immunocompromised, the cancer cells will be attacked by the host's immune system, be destroyed and fail to create a tumor. The specification does not teach how to use an animal that rejects the cancer cells.

Claims 14, 16, 18 and 20 are drawn to a method of selecting agents that treat tumors by administering a test substance to an animal before and/or after transplanting cancer cells. The claims refer to the method of claim 1; however, the claims are unclear (see 112/2nd). For this rejection, it is assumed the claims are directed to a method of using animals made by the method of claim 1. The claims are not enabled because the specification does not provide adequate guidance how to perform the method by teaching the specific steps of administering agents, the controls or how to compare the results so that agents that treat cancer are identified. Without such guidance, applicants have left those of skill with undue experimentation to determine the steps for using animals made by the method of claim 1 to identify agents that treat cancer. Clarification is required.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it is unclear what applicants consider the hydration force of a polymer and a polymer that "changes its hydration force in a temperature range of 0-80˚C". The metes and bounds of hydration force and polymers that change their hydration force from 0-80˚C are not defined in the specification or the art at the time of filing. Therefore, those of skill would not know when they were using a polymer that infringed on the claim.

The temperature "region wherein the polymer has weak hydration force" in claim 1 is indefinite. The metes and bounds of when a hydration force is "weak" is not defined in the specification or art at the time of filing. The specification does not teach how to determine when a polymer is in a temperature range that causes a weak hydration force. Without such guidance, those of skill would not be able to determine when they were infringing on the claim.

Likewise, the temperature "at which the polymer has a stronger hydration force" in claim 1 is indefinite. The metes and bounds of when a hydration force is "stronger" is not defined in the specification or art at the time of filing. The specification does not teach how to determine when a polymer is in a temperature range that causes a stronger hydration force. Without such guidance, those of skill would not be able to determine when they were infringing on the claim.

Claim 1 is indefinite because it states the cultured cancer cells are "detached" but does not clearly set forth whether they are "detached" from the cell culture support, the polymer or both.

The metes and bounds of what applicants consider a specified site in claim 1 is indefinite. It cannot be determined how the adjective "specified" qualifies the structure or function of the site receiving the cancer cell transplant.

The metes and bounds of what applicants consider a "sheet" of a cancer cells in claims 2 and 3 cannot be determined. It cannot be determined when cancer cells have formed a sheet. The structure of a sheet of cells is not defined in the specification or the art at the time of filing. Therefore, those of skill would not be able to determine when they were infringing on the claim.

Claim 3 is indefinite because the metes and bounds of what applicants consider a specified shape of a specified size is indefinite. It cannot be determined how the adjective "specified" qualifies the structure or function of the size or shape of the sheet of cancer cells. The phrase goes on to say "so that the size and/or shape of the cancer tissue transplanted into the animal is controlled"; however, it cannot be determined what applicants consider controlled, and the phrase "the cancer tissue transplanted" lacks antecedent basis. The "so that…" phrase does not clearly set forth the size and/or shape of the cancer cell sheet. Therefore, it does not appear that claim 3 further limits claim 2 in any way because any size and/or shape put into the animal has been prepared in a specific shape and size and is controlled.

The metes and bounds of what applicants consider "intimate contact" in claim 5 is indefinite. It cannot be determined how the adjective "intimate" qualifies the contact. How intimate is intimate?

Claim 6 is indefinite because the metes and bounds of when a cancer cell is from a "transplantable" cell line. It cannot be determined how "transplantable" qualifies the cell line because all cancer cell lines are transplantable.

Claim 7 is indefinite because the metes and bounds of when a cancer cell is from an "untransplantable" cell line. It cannot be determined how "untransplantable" qualifies the cell line because all cancer cell lines are transplantable.

The metes and bounds of claim 9 are indefinite because all cells are collected from once living tissue.

Claims 14, 16, 18 and 20 are indefinite because they do not clearly set forth how to select anti-tumor agents using the animal of claim 1. The claims do not clearly set forth how to select agents that treat or prevent tumors by comparison to a control or in the same animal over a period of time. The numerous embodiments for testing agents using the animals encompassed by the claims are so vague as to be meaningless. For example, if the animal develops a tumor and agents are screened for treating the tumor, the claim must set forth the animal develops a tumor, an agent is administered to the animal, parameters of the control and a clear step explaining how to determine agents that treat the tumor. Clarification is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4-7, 9, 12, 13, 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Koezuka (Nippon Nogei Kagaku Kaishi, 1994, Vol. 68, No. 4, pg 783-792, abstract only).

Koezuka taught culturing cancer cells from a primary culture on a thermoresponsive polymer, detaching the cells from the polymer without trypsin and transplanting the cells to nude mice. Claim 5 is included because it is unclear what applicants consider intimate. Claims 6 and 7 are included because the primary culture described by Koezuka is either a transplantable or untransplantable cell line.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-13, 15, 16, 17 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koezuka (Nippon Nogei Kagaku Kaishi, 1994, Vol. 68, No. 4, pg 783-792, abstract only) in view of JP 05/192138.

Koezuka taught culturing cancer cells on a thermoresponsive polymer and transplanting the cells into nude mice. The abstract of Koezuka did not teach using poly(N-isopropylacrylamide) polymer.

However, methods of culturing cells with poly (N-isopropylacrylamide) were known in the art. The specification states JP 05/192138 taught a method of "skin cells cultivation comprising the steps of preparing a cell culture support which has a surface of its base coated with a polymer having an upper or lower critical temperature for dissolution in water in a range of 0-80°C, cultivating skin cells on the cell culture support

at a temperature not higher than the upper critical temperature for dissolution or at a temperature not lower than the lower critical temperature for dissolution, and thereafter adjusting the temperature to above the upper critical temperature for dissolution or below the lower critical temperature for dissolution, whereby the cultured skin cells are detached. This method depends on temperature adjustment for detaching the cells from the culture base coated with the temperature-responsive polymer." A translator at the patent office confirmed the patent discusses using poly (N-isopropylacrylamide) as the polymer and states 90% of cells could be peeled off in a sheet.

Thus, it would have been obvious to those of ordinary skill in the art at the time the invention was made to culturing cancer cells on a thermoresponsive polymer and transplant the cells into nude mice as taught by Koezuka wherein the culturing was performed using the poly (N-isopropylacrylamide) described in JP 05/192138. Those of ordinary skill in the art would have been motivated to use the poly (N-isopropylacrylamide) described in JP 05/192138 to culture the cancer cells because the method by Koezuka showed 90% of the cells could be peeled off in a sheet.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

/Michael C. Wilson/
Patent Examiner